REMARKS

Claims 1, 2, 6, 7, and 9-24 are pending. Claims 2, 6, 7, 9, and 16-18 have been amended. New claims 19-24 have been added. Support for the new claims can be found throughout the application as originally filed. No new matter has been added.

Applicants also submit herewith a copy of an English abstract for European patent application 0 475 354 cited in the Information Disclosure Statement filed April 6, 2000. Therefore, Applicants respectfully request that the Examiner consider this reference.

Rejection of Claims 1-18 Under the Doctrine of Obviousness-Type Double Patenting

Claims 1-18 remain rejected under the judicially created doctrine of obviousness-type double patenting. In particular, the Examiner states that "it is acknowledged that the terminal disclaimer along with the response was received on June 23, 2000 in Paper No. 8. However, a check of $110 was not enclosed for the required fee."

Applicants note that the response filed June 23, 2000 requested that the deposit account be charged for any additional fees. Therefore, the Examiner had permission to charge the deposit account for this fee. Regardless, Applicants enclose herewith a check for $110 for the terminal disclaimer fee. Applicants request that the Examiner enter the Terminal Disclaimer filed on June 23, 2000 into the record, and withdraw this rejection.

Rejection of Claims 1, 2, and 6-18 Under 35 U.S.C. §112, first paragraph

Claims 1, 2 and 6-18 are rejected under 35 U.S.C. §112, first paragraph, because "the specification while being enabling for antithrombin III having a specific glycosylation pattern and obtained from transgenic goat milk, does not reasonably provide enablement for any antithrombin III having glycosylation differences and obtained from any transgenic mammal." In particular, the Examiner states that

> Applicant's specification does not provide any guidance to the artisan on the phenotypic outcome of antithrombin III produced by the transgenic mouse or

any other mammal as broadly claimed. Applicant's specification supports the N-linked glycosylation for tgATIII was more heterogenous than phATIII, which a higher degree of fucosylation and more varied sialyation (page 19 and Table 3), for example. Applicants argues that at page 8, lines 4-22, the specification described the production of transgenic mice by microinjected of the BC6 transgene which is the same transgene used to produce the transgenic goat. There is no evidence of record which supports that transgenic mice microinjected with a 14.95 Kb transgene (Bc6) into mouse embryos and a transgenic goat produced by the same 14.95 Kb transgene (Bc6) would produce the same antithrombin III glycosylation pattern protein. Although the specification compares the antithrombin III produced in the transgenic goat with the plasma derived hATIII, there is no evidence that the transgenic mouse results in the same phenotypic outcome when different patterns of glycosylation is observed between human and transgenic goat derived antithrombin III.

The Examiner further states that

The intention of the animal model, as defined in the specification of the instant application, is for transgenically producing antithrombin III in goat's milk comprising monosaccharides having a specific glycosylation pattern. The claims read on any glycosylation pattern of antithrombin III that differs from that found in human plasma, but the specification only teaches specific glycosylation patterns of a goat produced antithrombin III. Given such a distinction in the glycosylation pattern to host in the expression of antithrombin III, it would require undue experimentation to generate a general model that exhibits all the glycosylation pattern seen in any transgenic mammal or any glycosylation pattern of antithrombin III. It is standardly and well known in the art that glycosylation patterns are a function of the host cell in which the protein product is translated and post-translationally modified by the host enzymes. There is insufficient objective evidence provided to indicate that the numerous embodiments of different glycosylation patterns now claimed would be predictably obtainable from a goat host or any other host. . . .

In the instant case, there is no evidence of record which suggests that the mouse transgenically produced antithrombin III would have the same glycosylation pattern as compared to a transgenic goat or any other mammalian species as embraced by the claims. Thus, the evidence of a transgenic mouse without the phenotypic outcome of antithrombin III produced by the transgenic goat is not sufficient to enable any and all mammal.

Applicants respectfully traverse this rejection. The Examiner incorrectly states that the claims are directed to "any antithrombin III" obtained from any transgenic mammal and that the claims read on any glycosylation pattern that differs from plasma derived antithrombin III. Instead, the claims are directed to mammary gland produced antithrombin III having a monosaccharide composition which differs from plasma derived antithrombin III. The claims are limited to antithrombin III, having one or more of the following distinguishing characteristics: the presence of GalNAc (plasma derived antithrombin III lacks GalNAc); the presence of fucose (plasma derived antithrombin III is not fucosylated); and/or having a higher level of oligomannose or hybrid mannose structure than does plasma derived antithrombin III.

As provided in the Declaration of Carol Ziomek, Ph.D., Under 37 CFR 1.131 (hereafter referred to as "the Declaration of Dr. Ziomek"), Applicants have shown that the claimed glycosylation patterns occur in mammary gland produced antithrombin III of very divergent species, namely goat and mouse. Thus, Applicants have enabled a broad claim to mammary production in mammals. Further, Applicants have shown, by way of a number of comparisons that the differences are organ and not species specific. The substitution of GalNAc for galactose is the function of expressing ATIII in the mammary gland and not a species difference particular to goat. It was also disclosed that the presence of fucose and the higher levels of oligomannose and hybrid mannose structures are found in mammary gland produced antithrombin III as compared to plasma derived antithrombin III. This has been further evidenced by the results provided the Declaration of Dr. Ziomek. Since Applicants describe a transgene which encodes antithrombin III and is expressed in the mammary gland of different species of transgenic mammals, and antithrombin III produced in the mammary tissue has the claimed monosaccharide compositions as further evidenced by the Declaration of Dr. Ziomek, there is clearly sufficient guidance to make and use the claimed mammary gland produced antithrombin III. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

Rejection of Claim 18 Under 35 U.S.C. §112, second paragraph

Claim 18 is rejected under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner states that "claim 18 is vague and indefinite in its recitation of 'faster clearance time' because it is unclear from the specification as to what is encompassed in the claims as to how fast is faster. The metes and bounds can not be determined."

Claim 18 has been amended thereby obviating this rejection.

Rejection of Claims 1, and 6-7 Under 35 U.S.C. §102(a)

Claims 1 and 6-7 are rejected under 35 U.S.C. §102(a) as being anticipated by Cole et al. (1994) *J. Cellular Biochemstry Suppl.* 0(18D):265. According to the Examiner,

> As to the discussion of the Cole declarations under 37 C.F.R. 1.132, both declarations are ineffective under In re Katz because the two declarations remove the names of Higgens, Bernasconi, Gerone, and Edmunds leaving only author Cole. Cole alone, is not identical to the inventive entity of DiTullio, Meade and Cole and is legally another to the present inventive entity. The In re Katz is further insufficient in that it does not clearly state DiTullio and Meade contribution to the inventive concept of the claimed invention.

Applicants respectfully disagree that the Declaration of Cole Under 37 CFR 1.132 is ineffective as an In re Katz declaration. First of all, Applicants respectfully disagree with the Examiner's statement that the Declaration of Cole does not clearly state that DiTullio and Meade are inventors. The first section of the Declaration of Cole states that Cole is a co-inventor with Meade and DiTullio of the present application. This is sufficient to establish inventive contribution by Meade and DiTullio, especially in view of the fact that all three inventors, Cole, Meade and DiTullio signed a Declaration Under 37 CFR 1.63 establishing that they were joint inventors of the present application. Secondly, not all of the inventors need to be authors for an In re Katz declaration to be sufficient. This is clearly set forth in the MPEP section 2132.01. See e.g., the discussion of *Ex parte Kroger*, 219 USPQ 370 (Bd.

Pat. App. & Inter. 1982). Therefore, Applicants respectfully request that the Examiner enter the Declaration of Cole Under 37 CFR 1.132 as previously filed, and withdraw this rejection.

Conclusion

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Enclosed are a check for excess claim fees and a $1960 check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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Version with markings to show changes made

In the claims:

Claim 2, 6, 7, 9 and 16-18 has been amended as follows:

2. (Amended) Mammary gland produced antithrombin III having a monosaccharide composition which comprises [GalNAc and which lacks O-linked glycosylation] fucose.

6. (Amended) Mammary gland produced antithrombin III [comprising] having a monosaccharide composition which [is partially sialylated] comprises a higher level of mannose than plasma derived antithrombin III.

7. (Amended) The [Mammary] mammary gland produced antithrombin III of claim 1 [having a monosaccharide composition] further comprising [sialic acid which includes NGNA] fucose.

9. (Amended) The mammary gland produced antithrombin III of claims 1, 2, [6,] or 7 wherein the antithrombin III [is produced in the mammary glands of a transgenic mammal] further comprises a higher level of mannose than plasma derived antithrombin III.

16. (Amended) [The] A glycosylated human antithrombin III [of claim 15] which is produced in the mammary gland of a non-human transgenic mammal, wherein the antithrombin III [further] comprises a monosaccharide composition which [is partially sialyated] comprises fucose.

17. (Amended) [The] A glycosylated human antithrombin III [of claim 15] which is produced in the mammary gland of a non-human transgenic mammal, wherein the antithrombin

III [further] comprises a monosaccharide composition [comprising sialic acid] which [includes NGNA] comprises a higher level of mannose than plasma derived antithrombin III.

18. (Amended) The glycosylated human antithrombin III of claim [16 or] 17, wherein the antithrombin III has a [faster clearance time of at least 4 fold] higher affinity for heparin binding as compared to plasma derived antithrombin III.

Please add claims 19-24.

--19. (New) A method for producing antithrombin III in mammalian milk, comprising:

providing a transgenic mammal that expresses in its mammary tissue a transgene which encodes a human antithrombin III with a monosaccharide composition which comprises fucose, wherein said human antithrombin III is secreted into the milk of the mammal; and

collecting milk from the transgenic animal which contains the human antithrombin III

to thereby obtain human antithrombin III with a monosaccharide composition which includes fucose.

20. (New) The method of claim 19, wherein the transgenic mammal is a goat.

21. (New) The method of claim 19, wherein the transgenic mammal is a mouse.

22. (New) A method for producing antithrombin III in mammalian milk, comprising:

providing a transgenic mammal that expresses in its mammary tissue a transgene which encodes a human antithrombin III having a monosaccharide composition which comprises a higher level of mannose than plasma derived antithrombin III, wherein said human antithrombin III is secreted into the milk of the mammal; and

collecting milk from the transgenic animal which contains the human antithrombin III

to thereby obtain human antithrombin III having a monosaccharide composition which includes a higher level of mannose than plasma derived antithrombin III.

23. (New) The method of claim 22, wherein the transgenic mammal is a goat.

24. (New) The method of claim 22, wherein the transgenic mammal is a mouse.--